Technology in Cancer Research & Treatment
Volume 17: 1-8

DOI: 10.1177/1533033818798633
journals.sagepub.com/home/tct

A Systematic Literature Review on Salvage Radiotherapy for Local or Regional Recurrence After Previous Stereotactic Body Radiotherapy for Lung Cancer

Yukinori Matsuo, MD, PhD[1]

Abstract

Purpose: The purpose of this review article was to summarize available data on the efficacy and safety of salvage radiotherapy for isolated local or regional recurrence after prior stereotactic body radiotherapy for lung cancer. **Methods:** Studies were systematically searched on PubMed, following which suitable papers were selected. Reported outcomes and toxicities were qualitatively reviewed. **Results:** Nineteen papers, which were retrospective studies based on single institution experiences, were selected. Sixteen papers were on salvage radiotherapy for local tumor recurrence, and the remaining 3 papers evaluated radiotherapy for regional failures after stereotactic body radiotherapy for lung cancer. Patient cohorts in the selected papers seemed very frail with 2-year survival of 30% to 40% after the salvage. Local control was reported to be approximately 60% to 70%, which is worse than that after primary stereotactic body radiotherapy. Reported rates of toxicity grade 3 or worse were considered acceptable. Larger target volume and central tumor localization were suggested as risk factors for severe toxicities. Dosimetric data on patients having toxicities were found to help with considering dose constraints for organs at risk. **Conclusion:** Based on data from a limited number of articles, salvage radiotherapy is a reasonable treatment option for select patients with local or regional tumor recurrence after prior stereotactic body radiotherapy for lung cancer. Optimal patient selection and dose prescription can be clarified with a larger study that include more data on experiences with salvage radiotherapy.

Keywords

re-irradiation, stereotactic body radiotherapy, lung cancer, local recurrence, regional recurrence

Abbreviations

BED, biologically effective dose; CFRT, conventionally fractionated radiotherapy; CT, computed tomography; CTV, clinical target volume; EQD2, equivalent dose in 2-Gy fractions; JCOG, Japan Clinical Oncology Group; NSCLC, non-small-cell lung cancer; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiotherapy; VCP, vocal cord paralysis

Received: February 23, 2018; Revised: May 29, 2018; Accepted: August 08, 2018.

Introduction

Stereotactic body radiotherapy (SBRT) is now an important treatment option for patients with early-stage non-small-cell lung cancer (NSCLC), especially for medically inoperable patients.[1] Several prospective trials have proven the efficacy and safety of SBRT for early-stage NSCLC. The Japan Clinical Oncology Group (JCOG) 0403 was a prospective multi-institutional phase 2 trial for SBRT for stage IA NSCLC in both medically inoperable and operable patients.[2] The JCOG 0403 evaluated outcomes of 100 inoperable and 64 operable (total 164) patients with a median age of 78 years (range: 50-91 years). Of the 100 inoperable patients, overall survival was 59.9% and 76.5% at 3 years for the inoperable and operable patients, respectively. The local control rate at 3 years was

[1] Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Corresponding Author:
Yukinori Matsuo, MD, PhD, Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Sakyo, Kyoto 6068507, Japan.
Email: ymatsuo@kuhp.kyoto-u.ac.jp

87.3% and 85.4%, respectively. No grade 5 toxicity was observed. Other multi-institutional phase 2 trials, including the Radiation Therapy Oncology Group (RTOG) trial 0236[3] and the Nordic study group trial,[4] have also proven the efficacy and safety of SBRT for medically inoperable patients.

The dominant pattern of failure after lung SBRT is distant metastasis. However, a few patients develop local tumor recurrence or isolated regional lymph node metastasis. Local tumor recurrence, lymph node metastasis, and distant metastasis were observed in 20, 24, and 44 patients, respectively, in the JCOG 0403 and in 3, 2, and 11 of 59 patients in the RTOG 0236, respectively. The efficacy and safety of salvage surgery for isolated local recurrence have been recently reported by several studies.[5-11] However, the indications for salvage surgery are very limited because most SBRT patients are medically inoperable. Salvage SBRT is an attractive option for the medically inoperable patients with isolated local recurrence. Regarding regional failure, an international consortium of expert radiation oncologists discussed treatment recommendations for a case with recurrent node-positive NSCLC after previous SBRT for stage I disease.[12] All the experts agreed that salvage chemoradiotherapy is not contraindicated in such a case. However, no consensus was made regarding radiotherapy (RT) dose and fractionation used for the patient.

Few data are available on salvage RT for local or regional failures after lung SBRT. The purpose of this review article was to search relevant papers systematically and to summarize available data from studies on efficacy and safety of salvage RT for isolated local or regional recurrence after prior SBRT for lung cancer.

Materials and Methods

Potential studies for the present review were systematically searched on PubMed using key search terms shown in Table 1. Inclusion criteria were as follows: (1) studies that included patients with primary lung cancer or a metastatic lung tumor that was treated, (2) studies with at least one patient who underwent SBRT as an initial treatment for the tumor, and (3) studies that reported on salvage RT performed for local or regional recurrence after the initial treatment. Reported outcomes and toxicities were qualitatively reviewed in the present article.

To help with the comparison of doses that had different fractionations, the prescribed doses were converted into equivalent doses in 2-Gy fractions (EQD2). The EQD2 was given by the following formula with a fractional dose of d [Gy], a number of fractions of n, and an alpha-beta ratio of α/β [Gy]:

$$\mathrm{EQD2} = nd \times \frac{d + \alpha/\beta}{2 + \alpha/\beta}.$$

We applied an α/β of 10 Gy to calculate EQD2 [Gy_{10}] for tumor response, and an α/β of 3 Gy for late normal tissue toxicity EQD2 [Gy_3], respectively. When biologically effective doses (BED) were provided in the article, the BED was converted into EQD2 with the formula:

$$\mathrm{EQD2} = \mathrm{BED} \times \frac{\alpha/\beta}{2 + \alpha/\beta}.$$

Table 1. Search Words Used for Identifying Articles in PubMed.

Logical Connection	Keywords
	(Lung Neoplasms[MeSH Terms]) OR lung cancer
AND	((stereotactic body radiotherapy) OR stereotactic body radiation therapy) OR stereotactic ablative radiotherapy
AND	((re-irradiation) OR reirradiation) OR salvage radiotherapy
NOT	(brain metastasis) OR brain metastases
NOT	Review[Publication Type]

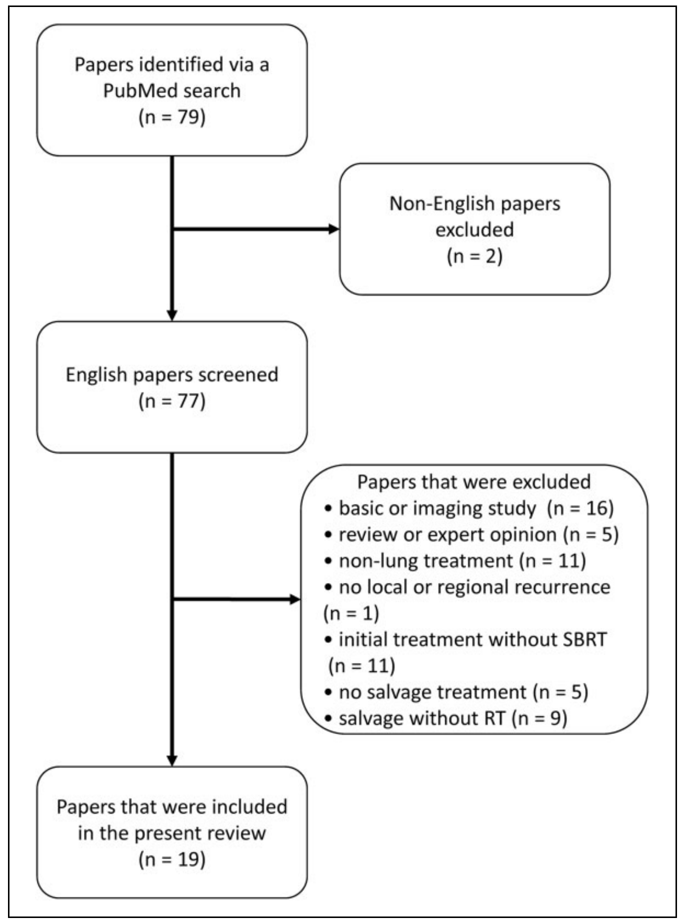

Figure 1. Flow diagram for the selection of papers.

Results

Seventy-nine potential papers were identified through the PubMed search on January 31, 2018. Nineteen articles satisfied the abovementioned criteria (Figure 1). The 19 articles were all retrospective studies based on single institution experiences. Sixteen papers were on salvage RT for local tumor recurrence,

Table 2. Reports on Salvage Radiotherapy for Local Tumor Recurrence After Prior Stereotactic Body Radiotherapy for Primary or Metastatic Lung Tumors.[a]

Author (Year)	Peulen *et al* (2011)[15]	Valakh *et al* (2013)[16]	Yoshitake *et al* (2013)[17]	Hearn *et al* (2014)[18]
No. of patients (lesions)	29 (32)	9 (9)	17[b]	10 (10)
Sex (M:F)	18:11	NR	15:2	5:5
Age, years	65 (18-87)	74 (59-83)	81 (69-88)	72 (51-78)
Tumor type (primary: metastatic)	6:23	8:1	17:0	10:0
Tumor location (central: periphery)	11:21	0:9	NR	2:8
Initial treatment				
Tumor size, cm	PTV, 71 (7-150) (cm^3)	2.39 (1.3-3.1)	2.8 (1.0-5.1)	2.2 (1.0-4.5)
Regimen	SBRT, 20-45 Gy/2-5fx	SBRT, 30-60 Gy/3-5fx	SBRT, 48-60 Gy/4-10fx	SBRT, 30-50 Gy/1-5fx
EQD2 [Gy_{10}]	CTV mean, 109 (49-163)	110.0 (50.0-150.0)	88.0 (80.0-88.0)	83.3 (83.3-124.7)
Time to salvage treatment, mo	14 (5-54)	11 (1-25)	12.4 (6.3-35.5)	14.8(9.9-26.3)
Salvage treatment				
Tumor size, cm	PTV, 76 (16-355) (cm^3)	1.98 (1.1-4.2)	4.1 (1.9-7.7)	3.4 (1.7-4.8)
Regimen	SBRT, 20-45 Gy/1-5fx	SBRT, 30-60 Gy/3-5fx	CFRT, 60-70 Gy/30-35fx	SBRT, 50-60 Gy/3-5fx
EQD2 [Gy_{10}]	CTV mean, 109 (79-163)	110.0 (50.0-150.0)	60.0 (60.0-70.0)	83.3 (83.3-150.0)
Use of concurrent chemotherapy	12 (41%)	NR	4 (23.5%)	NR
Follow-up from the salvage, mo	12 (1-97)	22 (4-40)	12.6 (4.3-31.1)	13.8 (5.3-43.5)
Local control	52% at 5 mo	75% at 2 years	LPFS 33.8% at 1 year	60%
Survival	59% at 1 year, 43% at 2 years	68.6% at 2 years	74.7% at 1 year	3 NED
Toxicity				
Grade 2	12 (RP, pleural effusion, etc)	3 (CWP, RP, BrP)	1 (rib fracture)	(3 Gr1-2 fatigue, 5 Gr1-2 CWP)
Grade 3	5 (RP, dermatitis, CWP, etc)	3 (dyspnea, CWP)	none	none
Grade 4	1 (SVC occlusion, tracheal fistula)	none	none	none
Grade 5	3 (bleeding)	none	none	none

Abbreviations: BrP, brachial plexopathy; CFRT, conventionally fractionated radiotherapy; CTV, clinical target volume; CWP, chest wall pain; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; LPFS, local progression-free survival; mo, months; NED, alive with no evidence of disease; NR, not reported; PTV, planning target volume; RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy; SVC, superior vena cava.
[a]Values are shown in median (range), if unspecified.
[b]Including 4 patients who had regional or distant metastasis in addition to local recurrence.

and the remaining 3 papers evaluated RT for regional failures after SBRT for lung cancer.

Salvage RT for Local Tumor Recurrence

Two papers evaluated patterns of failure after SBRT for early-stage NSCLC and the application rate of salvage treatment to patients with isolated local or regional tumor recurrence.[13,14] Hamamoto *et al*[13] administered SBRT to 86 patients with stage I NSCLC between 2006 and 2009. With a median follow-up period of 26 months, 10 (11.6%) local failures and 3 (3.5%) regional lymph-node failures were observed. Curative-intent salvage treatment was delivered to 7 of the 10 local failures, including RT and surgery for 5 and 2 local failures, respectively. Overall survival at 1 and 2 years after the local salvage treatment was 60% and 0% for the RT group ($n = 5$), and 100% and 100% for the surgery group ($n = 2$), respectively. No patients with regional failure received curative-intent treatment. Verstegen *et al*[14] reviewed 855 patients who received SBRT for early-stage NSCLC. Isolated locoregional recurrence was observed in 31 (3.6%) patients. Among them, 5 patients underwent salvage surgery while 4 received RT. The median overall survival was 36 months in those who received such radical treatment.

Four papers retrospectively investigated efficacy and safety of salvage RT for local tumor recurrence in patients who had received prior definitive SBRT for primary lung cancer or metastatic lung tumors[15-18] (Table 2). Peulen *et al*[15] from Karolinska University Hospital published the first report on salvage SBRT for local recurrence after previous SBRT. Patients in their study were given a median reirradiation EQD2 of 109 Gy. The report consisted of 29 patients with 32 lesions. Eleven lesions were centrally located. Nine patients had severe (grade 3 or worse) toxicities with a median time of 4 months (range: 1-39 months) from reirradiation. These toxicities included fatal bleeding in 3 patients. Larger clinical target volume (CTV) and central tumor localization were associated with more toxicity. Valakh *et al*[16] delivered salvage SBRT to 9 patients who had local recurrence in the lung periphery after prior SBRT. The salvage SBRT irradiation was performed under cone-beam computed tomography (CT) guidance. Local recurrence-free survival was 75% at 2 years. No grade 4-5 toxicities were observed. Yoshitake *et al*[17] from Kyushu University used conventional fractionated RT as a salvage treatment for 17 patients with local recurrence after SBRT for primary lung cancer. Four of the 17 patients also had metastasis to regional lymph nodes or the brain. The irradiation fields were limited to the recurrent gross tumors without elective nodal irradiation with a median dose of 60 Gy in 30 fractions. Concurrent chemotherapy was administered in 4 patients. Local progression-free survival was 33.8% at 1 year after the reirradiation. No grade 2 or worse toxicity was observed except in 1 patient with a grade 2 rib fracture. Hearn *et al*[18] reported their experience with salvage SBRT. They found that 22 patients who had isolated local recurrence after prior SBRT were not deemed candidates for the salvage therapy because of the following reasons: large tumor size (>8 cm); tumors were close to the mediastinum, chest wall, or proximal bronchus; history of overlapping conventional RT before initial SBRT; severe medical comorbidity; or persistent chest wall pain from initial SBRT. The remaining 10 patients with a recurrent tumor <5 cm received the re-SBRT with a median EQD2 of 83.3 Gy_{10} (range: 83.3-150.0 Gy_{10}). Three patients were alive without evidence of disease at the end of follow-up. There was no grade 3-5 toxicity.

Seven articles evaluated salvage RT for patients with local recurrence after previous thoracic irradiation that included not only SBRT but also conventionally fractionated RT (CFRT; Table 3). [19-25] Prescribed dose and fractionation varied among the articles. Trakul *et al*[19] assessed treatment outcomes for SBRT reirradiation for in-field recurrences after prior SBRT or CFRT. With a median BED of 80 Gy_{10} (EQD2, 66.7 Gy_{10}), the local control rate was 65.5% at 12 months. Improved local control was also associated with an interval time longer than 16 months between the treatments ($P = .042$). Ester *et al*[21] also reported SBRT salvage for isolated local recurrence after prior thoracic irradiation. Local control was 92% with a median survival of 24 months. Patel *et al*[23] evaluated treatment of in-field lung cancer recurrence with SBRT re-irradiation after CFRT or SBRT. SBRT reirradiation was delivered with a low median EQD2 of 40 Gy_{10}. The reirradiation resulted in no severe toxicities, and there was an acceptable crude local control rate of 80%. Ceylan *et al*[25] also reported on SBRT salvage for 28 patients with isolated local recurrence. They found a significant difference in local control between patients treated with BED $\geq$48 Gy_{10} (ECD2, 40 Gy_{10}) and those with BED <48 Gy (median local control, 48 months vs 13 months; $P = .007$). Meijneke *et al*[20] assessed accumulated dose and toxicity after reirradiation in 20 patients. There was no grade 3-5 toxicity observed. Median accumulated V20 (volume receiving 20 Gy or more) of the lungs was 15.2% (range: 3%-47%). In patients who received an accumulated dose higher than 70 Gy_3, a median EQD2 of the maximal dose was 115 Gy_3, 89 Gy_3, and 85 Gy_3 in the heart, the trachea and the esophagus, respectively. Kilburn *et al*[22] reported on their experience of thoracic reirradiation for local recurrence after prior RT. One patient developed an aortaesophageal fistula which is considered a grade 5 toxicity. The EQD2 in the aorta was estimated to be 200 Gy_3. Binkley *et al*[24] reported dose–volume data (D$x$cm^3, dose to the most exposed x cm^3) in patients who developed toxicities after thoracic reirradiation. The data included esophagitis $\geq$ grade 2 (D1cm^3, 41.0-100.6 Gy_3), chest wall $\geq$ grade 2 (D30 cm^3, 35.0-117.2 Gy_3), lung grade 2 (V20, 4.7%-21.7%), vocal cord paralysis (VCP; vagal nerve D0.2 cm^3, 207.5-302.2 Gy_3), and Horner syndrome (sympathetic trunk D0.2 cm^3, 130.8 Gy_3).

Regarding toxicity, 2 articles provided additional information. Shultz *et al*[26] reported clinical and dosimetric factors associated with VCP in patients treated with SBRT. They identified 2 patients who developed VCP; the first underwent repeat SBRT for a recurrent tumor in the left lung apex. Cumulative single fraction equivalent doses with an α/β of 3 ($SFED_3$) to the vagal nerve and the recurrent nerve were 37.4 Gy_3 and 13.7 Gy_3, respectively. The second patient, who had connective tissue disease, received $SFED_3$ of 16 Gy_3 and 19.5 Gy_3 to the vagal and recurrent nerves, respectively. They concluded that reirradiation and connective tissue disease are risk factors for VCP after SBRT for the lung. Nonaka *et al*[27] from the University of Yamanashi reported a case that demonstrated how 2 treatments with SBRT resulted in fatal gastric perforation. The patient in this case was an 83-year-old man who had T2N0M0 lung cancer in the base of the left lung. For the first treatment, SBRT was delivered with a dose of 40 Gy in 4 fractions. He developed a gastric ulcer at 3 months and was treated with medication. Following this, local tumor recurrence was observed at 8 months after the first treatment with SBRT. Re-irradiation with SBRT of 50 Gy in 4 fractions was delivered to the recurrent tumor with the patient well informed about the possibility of serious toxicity by the second treatment with SBRT. At 2 months after the second treatment with SBRT, fatal gastric perforation occurred. The maximal dose to the stomach was estimated to be 83.5 Gy in the nominal dose. Regarding optimal dose prescription for salvage SBRT, Nishimura *et al*[28] suggested that efficacy of SBRT with escalated dose to the tumor through a report of 2 cases. Two patients developed local recurrence in their lung periphery after prior SBRT with a prescription of 50 Gy in 5 fractions to an 80% isodose line. The salvage SBRT was performed with a dose of 60 Gy in 5 fractions prescribed to a 60% isodose line, which resulted in a higher dose at the tumor center with a steeper dose falloff outside the target volume than the prior prescription. Both patients in these cases achieved local control without severe toxicity.

Management of Regional Recurrence

We identified 3 articles that discussed management of regional recurrence after SBRT for the lung[29-31] (Table 4). Manabe *et al*[29] from Nagoya City University reported on their experience with salvage RT for hilar or mediastinal lymph node metastasis. The patient cohort consisted of not only post-SBRT (n = 13) but also postproton beam therapy (n = 1) and postsurgery

Table 3. Reports on Salvage Radiotherapy for Local Tumor Recurrence After Prior Radiotherapy for Primary or Metastatic Lung Tumor.[a]

Author (Year)	Trakul *et al* (2012)[19]	Meijneke *et al* (2013)[20]	Ester *et al* (2013)[21]	Kilburn *et al* (2014)[22]	Patel *et al* (2015)[23]	Binkley *et al* (2016)[24]	Ceylan *et al* (2017)[25]
No. of patients (lesions)	15 (17)	20 (20)	12 (13)	33	26 (29)	38 (44)	28 (34)
Sex (M:F)	7:10	14:6	8:4	19:14	19:7	23:15	25:3
Age, years	66 (49-92)	71 (50-80)	67.9 (45.9-86.7)	66 (45-80)	68 (42-87)	66 (35-94)	64 (48-90)
Tumor type (primary:metastatic)	12:5	17:3	11:1	29:4	26:0	31:7	28:0
Tumor location (central:peripheral)	6:11	NR	4:9	17:16	NR	26:12	16:18
Initial treatment							
GTV, cm^3	NR	26.5 (0.2-240)	NR	NR	NR	31.4 (0.8-248.5)	NR
Regimen	SBRT (n = 4), 25-50 Gy/1-4fx; CFRT (n = 11)	SBRT (n = 14), 30-60 Gy/1-6Fx; CFRT (n = 8), 45-60 Gy/15-25fx	SBRT (n = 2); CFRT (n = 10), 61.2 Gy (12-70 Gy)	SBRT (n = 10), 22.5-60 Gy/1-5fx; CFRT (n = 23), 45-80.5 Gy/28-37fx	SBRT (n = 3); CFRT (n = 23), 61.2 Gy (30-74 Gy)	SBRT (n = 21), 25-54 Gy; CFRT (n = 17), 45-71.6 Gy	SBRT (n = 1), 60 Gy; CFRT (n = 27), 59.4 Gy (47.5-66 Gy)
EQD2 [Gy_{10}]	72.9 (50-93.8)	133 (44-150)	NR	SBRT: 83.3; CFRT: 66	NR	72.9 (43.1-126)	NR
Time to salvage treatment, mo	16 (5-80)	17 (2-33)	19.7 (4.7-84.7)	18 (6-61)	8 (3-26)	16 (1-71)	14 (4-56)
Salvage treatment							
GTV, cm^3	14.2 (2-57.7)	20 (0.2-589)	4.6 (1.0-28.4)	2.5 (0.6-5.4) (cm)	3.2 (1.2-9.5) (cm)	9.1 (0.5-87.5)	24.2 (2.3-156.3)
Regimen	SBRT, 20-50 Gy/1-5fx	SBRT (n = 18), 32-60 Gy/3-6fx; CFRT (n = 2), 20-30 Gy/5-10fx	SBRT, 45-50 Gy/5fx	SBRT (n = 30), 20-54 Gy/1-10fx; CFRT (n = 3), 60-70.2 Gy/26-35fx	SBRT, 15-50 Gy/3-5fx	SBRT (n = 30), 25-50 Gy; CFRT (n = 14), 60-72 Gy	SBRT, 20-60 Gy/3-9fx
EQD2 [Gy_{10}]	66.7 (50.0-93.8)	83 (23-150)	71.3 (71.3-83.3)	SBRT: 83.3; CFRT: 70	40 (16.3-93.8)	72.9 (50.0-93.8)	46.9 (23.3-150.0)
Use of concurrent chemotherapy	NR	None	None	NR	NR	9 (24%)	16 (57%)
Follow-up from the salvage, mo	15 (4-65)	12 (2-52)	11.4 (1.6-38.3)	17		17 (3-57)	9 (3-93)
Local control	65.5% at 1 year	75% at 1 year; 50% at 2 years	92%	67% at 2 years	78.6% at 1 year; 65.5% at 2 years	88.3% at 1 year; 83.5% at 2 years	69% at 1 year; 37% at 2 years
Survival	80% at 1 year	67% at 1 year; 33% at 2 years	80% at 1 year; 36% at 2 years	76% at 1 year; 45% at 2 years	52.3% at 1 year; 37.0% at 2 years	79.6% at 1 year; 57.3% at 2 years	71% at 1 year; 42% at 2 years
Toxicity							
Grade 2	2 (CWP, VCP)	(4 dyspnea, 2 CWP, 2 dysphagia)	1 (atelectasis)	10 (6 CWP, 3 dyspnea, 1 esophagitis)	2 (cough, RP)	8 (lung, esophagitis, CWP)	1 (RP)
Grade 3		None	1 (RP)		None	6 (esophagitis, CWP, Horner syn., VCP, BrP)	None
Grade 4	None	None	None	None	None	None	None
Grade 5	None	None	None	1 (aortaesophageal fistula)	None	None	None

Abbreviations: BrP, brachial plexopathy; CFRT, conventionally fractionated radiotherapy; CWP, chest wall pain; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; GTV, gross tumor volume; NR, not reported; SBRT, stereotactic body radiotherapy; SVC, superior vena cava; syn., syndrome; RP, radiation pneumonitis; VCP, vocal cord paralysis.
[a]Values are shown in median (range), if unspecified.

Table 4. Reports on Salvage Radiotherapy for Isolated Regional Recurrence After Prior Treatment of Non-small-cell Lung Cancer.[a]

Author (Year)	Manabe *et al* (2012)[29]	Kilburn *et al* (2014)[30]	Ward *et al* (2016)[31]
No. of patients	26	12	15
Sex (M:F)	18:8	4:8	7:8
Age, years	75 (29-87)	66 (53-85)	77 (56-87)
Initial treatment	SBRT (n = 13), 48-52 Gy/4fx; Proton (n = 1), 60 GyE/10fx; Surgery (n = 12)	SBRT (n = 9), 50-60 Gy/3-5fx; AHRT (n = 2), 70.2 Gy/26fx; SBRT + AHRT (n = 1)	SBRT, 34-60 Gy/1-7fx
EQD2 [Gy_{10}]	90.9 (80.0-99.7)	83.3 (71.3-150.0)	85.7 (76.6-150.0)
Time to salvage treatment, mo	12 (1-62)	15 (2-57)	11.1 (1.8-39.0)
Salvage treatment	CFRT, 54-66 Gy/27-33fx	CFRT, 60-70.2 Gy/23-36fx	CFRT, 17-60.4 Gy/2-33fx
EQD2 [Gy_{10}]	64 (54-66)	66 (60-74.3)	48.8 (26.2-60.0)
Use of concurrent chemotherapy	3	2	2
Follow-up from the salvage, mo	35 (7-62)[b]	10 (2-49)	NR
Locoregional control	76% at 1 year (in-field)	100% at 2 years; 92% at 5 years	84.4% at 1 year
Survival	36% at 3 years (14% at 3 years for post-SBRT)	58% at 1 year; 29% at 2 years	73.3% at 1 year
Toxicity grade 2	8 RP, 2 esophagitis, 1 dermatitis	4 (esophagitis, dysphagia)	6 (5 esophagitis, 1 dyspnea)
Toxicity grade 3	1 dermatitis	1 (dyspnea)	None
Toxicity grade 4	None	None	None
Toxicity grade 5	1 RP	None	None

Abbreviations: AHRT, accelerated hypofraction radiotherapy; CFRT, conventionally fractionated radiotherapy; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; NR, not reported; RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy.
[a]Values are shown in median (range), if unspecified.
[b]Follow-up period for surviving patients.

(n = 12). They delivered a median of 64 Gy to recurrent tumors and 26 to 46 Gy for prophylactic therapy to the mediastinal lymph node area, respectively. The salvage RT resulted in in-field control of 76% at 1 year. Overall survival was 36% at 3 years for the whole cohort, and 14% for post-SBRT. One patient in the post-SBRT cohort had grade 5 radiation pneumonitis. Kilburn *et al*[30] retrospectively reviewed 12 patients who received salvage CFRT for isolated mediastinal failure after SBRT or hypofractionated RT. The median salvage dose was 66 Gy (range: 60-70 Gy) to the gross disease without elective nodal irradiation. The locoregional failure-free survival was 100% and 92% at 2 and 5 years, respectively. One patient developed grade 3 dyspnea, but no grade 4 or 5 toxicity was observed. The authors suggested that the omission of elective nodal irradiation resulted in a low toxicity rate. Ward *et al*[31] evaluated salvage RT for isolated nodal failure after SBRT. They used various dose regimens ranging from 17 Gy in 2 fractions to 60.4 Gy in 33 fractions. The most common regimen was 45 Gy in 15 fractions, which was used for 53% of the patients. The authors suggested that 45 Gy in 15 fractions might be ideal for many medically inoperable patients, but 60 Gy in 30 fractions with chemotherapy would be an option only for select patients.

Discussion

This review article aimed to summarize data from studies on the efficacy and safety of salvage RT for isolated local or regional recurrence after prior SBRT for lung cancer. The available articles were retrospective studies based on single institution settings. Patient characteristics and treatment regimens varied among the papers. Therefore, rigorous quantitative analysis of the data was impossible. Patient cohorts in the selected articles seemed very frail with 2-year survival of 30% to 40% after the salvage. Application rates of radical salvage treatment were limited to around a half or less in patients with isolated local recurrence.

A control rate of local tumor recurrence with salvage RT was reported to be approximately 60% to 70% (except in a few papers that reported higher rates), which was worse than that after primary SBRT (90%) as Trakul *et al* pointed out.[19] Because local recurrent tumors are thought possibly to be radioresistant, higher doses than the initial treatment might be needed to control the recurrent tumor. However, we also need to consider that the higher dose would result in a higher risk of severe toxicities. Although SBRT can be safely applied to recurrence in the lung periphery, those with central tumor recurrence or regional lymph node recurrence are not good candidates for salvage SBRT because of the risk of toxicities. All the 3 articles that discussed salvage RT for regional recurrence did not use SBRT but CFRT with or without chemotherapy.[29-31]

Toxicities after the salvage RT were found to be acceptable except for a few studies that reported grade 5 toxicities. To reduce the toxicity risk, we need to consider the 2 risk factors that include larger CTV and central tumor localization proposed by Peulen *et al*.[15] Dosimetric data provided by several

Table 5. Dosimetric Data in Patients Having Severe Toxicities After Reirradiation.

Toxicities	Organs At Risk	Maximal Dose in EQD2 [Gy_3]	Author (Year)
Aortaesophageal fistula grade 5	Aorta	200	Kilburn *et al* (2014)
Gastric perforation grade 5	Stomach	83.5 (nominal dose)	Nonaka *et al* (2017)
Esophagitis grade 3	Esophagus	D1 cm^3: 60.6	Binkley *et al* (2016)
Chest wall grade 3	Chest wall	D30 cm^3: 89.5, 124.6	Binkley *et al* (2016)
Vocal cord paralysis	Vagal nerve	D0.2 cm^3: 207.5, 302.2	Binkley *et al* (2016)
	Vagal nerve	37.4, 16 (SFED)	Shultz *et al* (2014)
	Recurrent nerve	13.7, 19.5 (SFED)	Shultz *et al* (2014)
Brachial plexopathy	Brachial plexus	D0.2 cm^3: 242.5	Binkley *et al* (2016)
Horner's syndrome	Sympathetic trunk	D0.2 cm^3: 130.8	Binkley *et al* (2016)

Abbreviations: D$x$cm^3, dose to the most exposed x cm^3; EQD2, equivalent dose in 2-Gy fractions; SFED, single fraction equivalent dose.

authors also help us to consider dose constraints for organs at risk (Table 5).

Surgery is also an important treatment option to salvage isolated local recurrence, if indicated. Neri *et al*[5] and Chen *et al*[6] made the first reports on salvage surgery for 7 and 5 patients, respectively, with local recurrence after SBRT. Both the articles reported that SBRT did not cause any difficulties in the surgical process. The efficacy and safety of salvage surgery for isolated local recurrence have been recently reported by several studies.[7-9] Taira *et al*[10] reported 2 patients who underwent salvage lung resection for suspected local recurrence after SBRT, which turned out to be no viable tumor. The report suggested difficulties in distinguishing local recurrence from post-SBRT changes. Hamaji *et al*[11] suggested that such a radical local treatment might result in better prognosis after local recurrence. They reviewed 49 patients with isolated local recurrence after SBRT, and 12 of them underwent salvage surgery. The results suggested that salvage surgery was associated with an improved overall survival of 79.5% at 5 years after the surgery ($P = .014$). Based on the report by Hamaji *et al*, surgery might be preferable as salvage treatment of local recurrence in the aspect of long-term survival. However, the indications for salvage surgery are very limited because most SBRT patients are medically inoperable.

Early diagnosis of local tumor recurrence is a key to reducing target volumes, which leads to a reduction in toxicity risk. However, it is not easy to distinguish local tumor recurrence from radiation-induced lung injury. Huang and Palma[32] recommends the following schedule of imaging for follow-up: serial CT imaging at 3 to 6 months for the initial year, then every 6 to 12 months for an additional 3 years, and annually thereafter. If local tumor recurrence is suspected, a multidisciplinary team discussion is recommended to evaluate the suspicious lesion based on the use of high-risk CT features and the uptake of 18-fluorodeoxyglucose on positron emission tomography. The high-risk CT features include (1) enlarging opacity at the primary site, (2) sequential enlarging opacity, (3) enlarging opacity after 12 months, (4) a bulging margin, (5) loss of linear margin, (6) air bronchogram loss, and (7) cranio-caudal growth.

In conclusion, based on data from a limited number of articles, salvage RT is a reasonable treatment option for select patients with local or regional recurrence after prior SBRT for lung cancer. Optimal patient selection and dose prescription can be clarified with a larger study that includes more data on experiences with salvage RT.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by JSPS KAKENHI Grant Number JP16H05389.

ORCID iD

Yukinori Matsuo, MD, PhD http://orcid.org/0000-0002-4372-8259

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